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Research Article

DEVELOPMENT, EVALUATION, AND CHARACTERIZATION OF LOSARTAN POTASSIUM BUCCAL PATCHES USING JACKFRUIT POLYMER

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ABSTRACT

Objective: The objective was to develop buccal patches of an antihypertensive drug and losartan potassium using jackfruit polymer for sustained buccal delivery.

Methods: The patches were prepared by the solvent casting method. Five formulations were developed with varying concentrations of jackfruit polymer. USP type II apparatus was used to perform *in-vitro* release study under perfect sink condition. Buccal formulations were developed to a satisfactory level in terms of drug release, bioadhesive strength, content uniformity, moisture content, surface pH, thickness, and stability study.

Results: From the results obtained F5 was found as best formulation, having appropriate folding endurance greater than 300, moisture content of 1.14±0.03 percentage (%), moisture uptake of 6.21±0.12%, swelling index (62.78%), bioadhesion strength (37.62±0.25 g), and bioadhesion time of 9 h 5 min. Fourier-transform infrared spectroscopy studies have shown no interactions between drug and polymer. All the formulations followed zero-order kinetics.

Conclusion: It can be concluded that mucoadhesive buccal patches of losartan potassium using jackfruit polymer are an auspicious dosage form to prolong the release of drug and enhance its poor oral bioavailability.

Keywords: Buccal patches, Jackfruit polymer, Solvent casting.

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INTRODUCTION

Mucoadhesion is a process of attachment between two materials such as mucosal membrane and mucoadhesive polymer for a protracted period. For the systemic and local administration of therapeutic agents, the buccal cavity is a supremely accepted site. The delivery of drugs through the buccal route gives direct entry to the systemic circulation through the jugular vein; thereby, it bypasses first-pass metabolism and degradation of the drug in the acidic environment of the gastrointestinal tract so that the drug's bioavailability gets enhanced [1,2].

In this modern epoch, lots of mucoadhesive devices have been developed. Buccal patches provide greater flexibility and comfort than buccal tablets. Furthermore, it can occupy on mucosa for more time compared to gels. Besides, it should possess sufficient mucoadhesive strength; thereby, it will keep hold in the mouth for a prolonged duration [3].

The natural polymers are widely used for various pharmaceutical preparations due to their certain advantages such as economy, ready availability, and nontoxicity [4]. Plentiful natural polymers such as pectin, guar gum, and chitosan are used as mucoadhesive polymers. The polymer which is extracted from fruits of *Artocarpus heterophyllus* (popularly called Jackfruit) belongs to the family *Moraceae*, which can act as a sustained release and mucoadhesive polymer [5,6].

Losartan potassium is an antihypertensive belongs to the classification of Angiotensin II receptor antagonist, which has low bioavailability due to extensive first-pass metabolism. Therefore, it is a satisfactory candidate for mucoadhesive buccal drug delivery [7]. By administering as a buccal drug delivery, desirable antihypertensive effects can be achieved by maintaining the losartan plasma concentration above the minimum effective concentration; thereby, we can reduce the dosage frequency to improve patient compliance [8]. This research work aims to design, formulate, and evaluate mucoadhesive buccal patches of losartan potassium-containing jackfruit polymer, to overcome its poor oral absorption and prolonging its release for the treatment of hypertension.

METHODS

Jackfruit was naturally collected from the Neyyar forest area of the district, Thiruvananthapuram. The plant of *A. heterophyllus* was authenticated by Dr. Sheeba M.S, Assistant Professor, Department of Botany, Government College for Women, Thiruvananthapuram. The herbarium voucher specimen number WC/121/2018 sample voucher specimen of the plant was deposited for future reference. Losartan potassium was a gift sample (Sangrose Laboratories, Alapuzha, India). HPMC K-100M, sucralose, ethylcellulose, and isopropyl alcohol were obtained from Yarrow Chem., Mumbai.

Isolation and purification of gum

The fruits were thoroughly washed to remove dirt and debris. Left overnight after incisions were made on them. The seeds were removed from the fruit. Then, the pulp was pressed and immersed in water for 5–6 h, boiled and allow to stand for 1 h for the entire release of the mucilage into the water. Then, using a multi-layer muslin cloth bag, the mucilage was extracted and marc was separated. Then, the supernatant was added with an excess volume of ethanol to precipitate the gum. The formed precipitate was dried in a hot air oven at 40–45°C. It is then collected, grounded, passed through a no. 120 sieve, and stored in a desiccator until use [4].

Identification of drug and drug-polymer interaction study

Fourier-transform infrared spectroscopy (FTIR) was carried on the drugs and the mixture of the drug and different polymers. Here

spectral changes in the mixture are the basis for the determination of compatibility.

Preparation of standard curve of losartan potassium

100 mg of losartan potassium was weighed and transferred into a 100 ml volumetric flask, which is then dissolved in a slight quantity of methanol and diluted with 6.8 phosphate buffer to produce a concentration of 1 mg/ml. 1 ml was taken from the stock solution in another volumetric flask and diluted up to 100 ml to give a stock solution 10 µg/ml. More dilutions were made from 2 to 10 µg/ml with a 6.8 phosphate buffer. The absorbance was measured at 235 nm [9].

Preparation of mucoadhesive buccal patches

Mucoadhesive buccal patches containing jackfruit mucilage were prepared by the solvent casting method. The drug and potassium (397.40 mg) were dissolved in 10 ml of water containing citric acid (0.5 mg) and sucralose by stirring on a magnetic stirrer for 1 h. A 10 ml solution of jackfruit gum in water was kept aside for 1 day to form a clear solution. HPMC K-100M was dissolved in 10 ml of acetone and added to the above solution. After stirring, mix the drug and polymer solution stirred for 1 h. The solution was then poured into a 9 cm glass petri dish and allowed to dry at 40°C in an oven. A solution of 500 mg of ethylcellulose and 0.2 ml dibutyl phthalate in 10 ml of acetone was poured to the petri dish to form a backing layer. It was air-dried, removed from the petri dish, packed in aluminum foil, and stored in a desiccator. Tables 1 and 2 show the composition of different buccal patches [10].

Evaluation of buccal patches of losartan potassium

Evaluation of physical parameters

Physical appearance and surface texture

It was performed by visual inspection of patches and evaluation of texture by feel or touch.

Weight variation test

The patch size of 2 × 2 cm^2 was cut. The weight of each patch was taken and the weight variation was calculated.

Thickness

The thicknesses of patches were measured using a screw gauge at different positions of the patch and the mean value was calculated [11].

Folding endurance

Folding endurance of the patches was measured by frequently folding one patch at the same place until it broke or folded up to 300 times manually. The number of times the patch could be folded at the same place without any breaking gave the result.

Measurement of surface pH

For the determination of surface pH, three films of each formulation were placed on the agar plate and allowed to swell for 2 h. The pH paper was placed over it and a mean of three readings was recorded [12].

Determination of moisture content and moisture absorption

Accurately, weighed buccal patches were placed in a desiccator containing anhydrous calcium chloride. After 3 days, it was taken out and weighed. The moisture content (%) was determined by:

$$\text{Moisture absorption}(\%) = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

A 100 ml saturated solution of aluminum chloride was taken in a desiccator for maintaining humidity and placed with accurately weighed patches. After 3 days, it was taken out and weighed [13]. The percentage of moisture absorption was calculated using the formula:

$$\text{Moisture absorption}(\%) = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Swelling studies

Previously weighed patches were placed over agar gel plate (2% w/v) and kept in an incubator at 37°C. A definite time intervals of 1, 2, 3, 4, 5, 6, 7, and 8 h, the weight of patches was determined [10]. The swelling index was found out using the formula:

$$S.I = \frac{W2 - W1}{W1} \times 100$$

Where, S.I. – swelling index

W1 – weight of buccal patch before dipping into the beaker

W2 – weight of buccal patch after dipping in beaker and wiped.

Evaluation of performance parameters

Drug content uniformity

Patches were dissolved in 5 ml ethyl alcohol and 2 ml of dichloromethane by homogenization for 5 h with occasional shaking and diluted to 50 ml with distilled water. It was then filtered to remove insoluble residue from the filtrate. 1 ml was taken and was diluted to 10 ml with pH 6.8 buffer. Using ultraviolet (UV) spectrophotometer absorbance was measured at 235 nm [14].

Ex-vivo bioadhesive strength

This study is used to measure the *in-vitro* bioadhesive capacity of various polymers. It is a modified method developed by Mertti Marvole [15]. Goat buccal mucosa was stored in a buffer of pH 6.8, within 3 h the experiment was performed. Then, the mucosa was tied to a glass slide with the help of a thread and was put in the petri dish containing 6.8 buffer solution kept at 37°C. The patch was pasted on to the glass stopper using cyanoacrylate glue and that stopper tied with a thread. The other portion of that thread was tied to the plastic container. That patch was put on mucosa by applying finger pressure for 30 s, then water was added through a pipe connected to a burette containing water in dropwise to that plastic beaker. Then, the weight of water required to detach the buccal patch from the mucosa was measured. The study performed shown in Fig. 1.

Ex-vivo bioadhesion time

Goat buccal mucosa was fixed inside the beaker above 2.5 cm from the bottom using cyanoacrylate glue. The patch was then pasted on to the mucosa by a light force by fingertip for 30 s. The beaker was filled with 500 ml of 6.8 buffer solution maintained at 37°C±1°C and was stirred at 50 rpm for 6 h. Then, the time taken by the patch to detach from the buccal mucosa was calculated as mucoadhesion time [16].

Table 1: Composition of losartan potassium mucoadhesive buccal patches

Formu-lationcode	Ingredients (mg)						
	Losartan potassium	Jackfruit Polymer	HPMC K-100M	Citric acid	Sucra-Lose	Propylene glycol (ml)	Dist.water (ml)
F1	397.40	50	300	0.5	0.5	1	10
F2	397.40	100	300	0.5	0.5	1	10
F3	397.40	150	300	0.5	0.5	1	10
F4	397.40	200	300	0.5	0.5	1	10
F5	397.40	250	300	0.5	0.5	1	10

HPMC: Hydroxypropyl methylcellulose

Ex-vivo permeation study

Ex-vivo drug permeation was performed using Franz diffusion cell. Goat buccal mucosa was placed between donor and receptor compartments and the temperature was maintained at 37±0.5°C. The patch was then placed over the membrane and the receptor compartment was filled with 15 ml of pH 6.8 phosphate buffer and stirred at 50 rpm. At definite time intervals (1, 2, 3, 4, 5, 6, 7, and 8 h), 1 ml aliquot was withdrawn and replaced with the same volume of fresh medium. Using UV spectrophotometer, the collected samples were analyzed at 235 nm after proper dilution [17].

Fig. 1: *Ex-vivo* bioadhesion strength

In-vitro dissolution study

The study was performed using the rotating paddle apparatus, maintained at 37±0.5°C, with a speed of 50 rpm. Buffer pH of 6.8 was used as a dissolution medium. Using cyanoacrylate glue, the backing layer of the patch adhered to a glass slide. Then, it was placed at the bottom of the vessel. 5 ml sample was withdrawn at predetermined time intervals and replaced with fresh medium. After appropriate dilution, it was filtered and analyzed by UV spectrophotometer at 235 nm [10].

Kinetic study

Here, the results obtained from *in vitro* release studies were plotted in different kinetics models of the data treatment as follows: Zero-order rate kinetics by plotting cumulative percentage drug release versus time, first-order rate kinetics by plotting log cumulative percentage drug retained versus time, and Higuchi's classical diffusion equation by plotting cumulative percentage drug release versus √T and Korsmeyer-Peppas by plotting log of cumulative percentage drug release versus log time [18].

Stability study

5 ml human saliva was taken in a petri dish and patches were placed over it. Then, it was kept in a temperature-controlled oven at 37°C±0.2°C for 8 h. A definite time intervals, morphological, and physical changes such as appearance, color, and shape were observed [19].

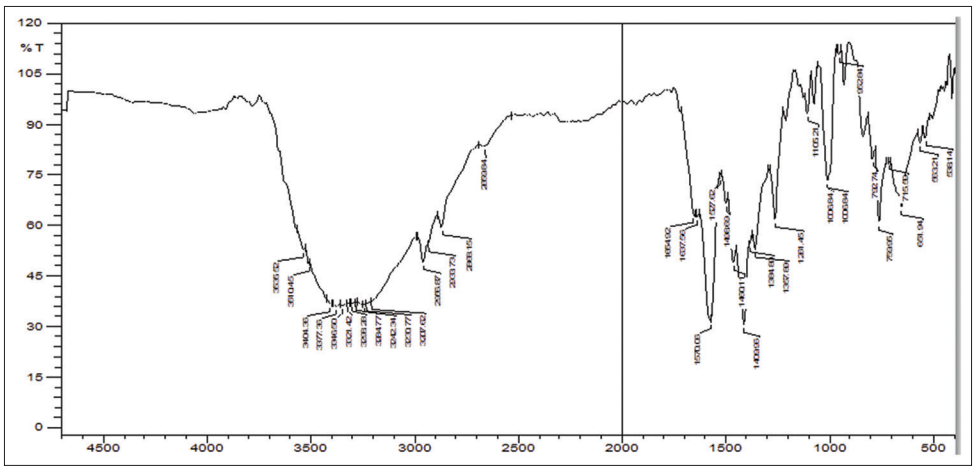

Fig. 2: Fourier-transform infrared spectroscopy spectrum of losartan potassium

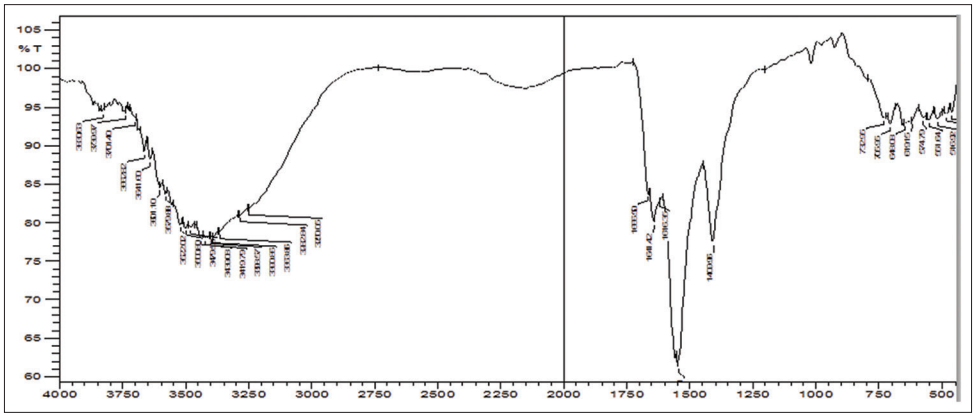

Fig. 3: Fourier-transform infrared spectroscopy spectrum of losartan potassium+jackfruit polymer+HPMC K 100M+ethyl cellulose

RESULTS AND DISCUSSION

Identification of drug and drug-polymer interaction study

The infrared spectroscopy (IR) spectrum of the drug alone and in combination with jackfruit mucilage, ethylcellulose, and HPMC K100M suggested that the characteristic peak of the drug was undisturbed and also the characteristic peak of the polymer was unaffected. Hence, the IR study indicates that drugs were in the free form and no drug-polymer and polymer-polymer interaction took place during formulation development. The IR spectra of drugs alone and in combination with the polymers are given in Figs. 2 and 3.

Standard curve of losartan potassium

The standard curve of losartan potassium was constructed in pH 6.8 buffer as the solvent system. Table 3 shows the absorbance readings of drug solutions containing 2–10 µg/ml of the drug in pH 6.8 buffer. Fig. 4 shows the standard curve for losartan potassium.

Table 2: Composition of backing membrane

Ingredient	Quantity
Ethyl cellulose	1.5 g
Acetone	19 ml
Isopropyl alcohol	11 ml
Dibutyl phthalate	2 ml

Table 3: Absorbance values of losartan potassium

Concentration (µg/ml)	Absorbance (nm)
0	0
2	0.1099
4	0.2246
6	0.3378
8	0.4398
10	0.5532

nm: nanometer

Table 4: Pre formulation study of isolated gum

S. No.	Parameters	Jackfruit polymer
1.	Macroscopic properties	
	Color	Light brown
	Odor	Odorless
2.	Solubility	
	Water	Soluble
	Ethanol	Insoluble
	Acetone	Insoluble
	Chloroform	Insoluble
3.	pH	6.7
4.	Angle of repose°	28.51
5.	Bulk density (g/cc)	0.52
6.	Tapped density (g/cc)	0.61
7.	Hausner's ratio	1.35
8.	Carr's index (%)	28.08

g/cc: Gram per cubic centimeter

Isolation and purification of gum

The mucilage from jackfruit isolated using appropriate extraction procedures (Fig. 5).

Characterization of mucilage

Macroscopic properties of mucilage such as color and odor were performed. It was soluble in water and insoluble in ethanol, acetone, and chloroform. pH, angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index were calculated. The results are shown in Table 4.

Physical appearance

All the buccal patches were visually inspected for clarity, flexibility, and surface texture. They are having good physical appearance. It is shown in Fig. 6.

Weight variation test

Weight uniformity of all the patches was determined by weighing three 2 × 2 cm^2 sections of each patch and then the average weight was calculated. All batches were uniform in weight and there was no significant difference. From the results shown in Table 5, the values were ranged from 88.97±0.18 to 103.41±0.42 mg.

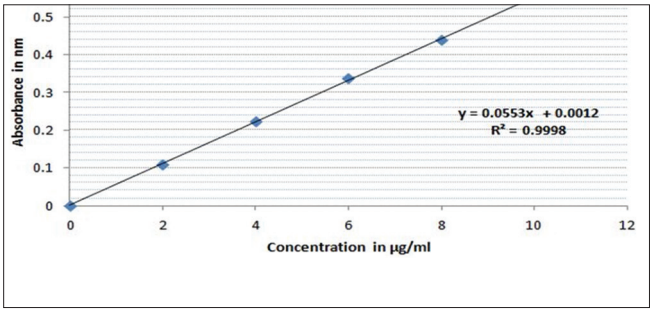

Fig. 4: Calibration curve of losartan potassium

Fig. 5: Jackfruit polymer

Table 5: Evaluation of physical parameters–average weight, thickness, folding endurance, and surface pH of losartan potassium mucoadhesive buccal patches

Formulation code	Average weight (mean±SD) (mg)	Thickness (mm)	Folding endurance	Surface pH
F1	88.97±0.18	0.11±0.05	276	6.11±0.15
F2	93.74±0.27	0.11±0.04	294	6.30±0.06
F3	97.12±0.34	0.13±0.02	>300	6.28±0.09
F4	100.24±0.26	0.14±0.06	>300	6.26±0.13
F5	103.41±0.42	0.16±0.07	>300	6.20±0.17

F: Formulation, SD: Standard deviation

Thickness

The average and standard deviation of all three readings were calculated and recorded in Table 5. It was found in the range of 0.11±0.05–0.16±0.07 mm. Thickness increases with an increase in the concentration of polymers.

Folding endurance

The recorded folding endurance of all the formulations was above the 200 and most of them are above 300, which indicates good flexibility. Table 5 shows the folding endurance value of all the formulations.

Measuring of surface pH

Table 5 shows the result of average surface pH values for all formulations. These values represent the mean of three replicate determinations. They were found to be in the range of 6.11±0.15–6.20±0.17. The results were within the limit of acceptable salivary pH range of 5.69–6.34 so that they may have less potential to irritate the buccal mucosa; thereby, patches will be compatible with the mucosa.

Determination of moisture content and moisture absorption

The moisture content (%) study was done for 3 days. The percentage of moisture content (%) is varied between 0.94±0.01 and 1.14±0.03% (Table 6). The moisture uptake values varied between 5.46±0.15 and 6.21±0.12% (Table 6). Low moisture content protects from microbial contamination and low moisture uptake (%) helps to retard hydrolytic degradation.

Table 6: Evaluation of physical parameter–moisture content (%) and moisture uptake (%) of losartan potassium mucoadhesive buccal patches

Formulation code	Moisture content (%)	Moisture uptake (%)
F1	0.94±0.01	5.46±0.15
F2	1.21±0.03	5.58±0.12
F3	0.93±0.04	5.73±0.19
F4	1.20±0.05	6.10±0.07
F5	1.14±0.03	6.21±0.12

%: Percentage

Table 7: Evaluation of physical parameters–swelling index of losartan potassium mucoadhesive buccal patches

Formulation code	Time (h)					
	1	2	3	4	5	6
F1	28.76	32.40	44.16	59.46	57.51	58.16
F2	36.45	38.71	45.06	56.90	58.37	58.15
F3	31.47	40.45	49.11	52.70	59.52	60.06
F4	26.74	37.98	51.26	54.67	58.52	61.80
F5	28.12	40.59	55.54	60.21	59.60	62.78

Swelling studies

Hydration and swelling of the patch are is necessary to initiate intimate contact of the patch with the mucosal surface. The adhesion increases with the increase in hydration up to a point. Excessive hydration may lead to an abrupt decline in adhesive strength. Overhydration can cause dilution of functional groups responsible for the adhesive interaction between the patch and mucosa. Swelling studies were performed to investigate the performance of the dosage form, swelling capacities, and patch integrity after swelling. Maximum swelling of 62.78% (F5) and minimum swelling of 58.15% (F2) were observed for patches. The swelling index of the patches increased with an increase in the polymer concentration. Table 7 shows the folding endurance value of all the formulations.

Drug content uniformity

The drug content of all the formulations was determined using a UV-visible spectrophotometer. Drug content was found to be in the range of 98.08±0.16–99.74±0.12%. The result showed that the drug was uniformly distributed throughout the patches and standard

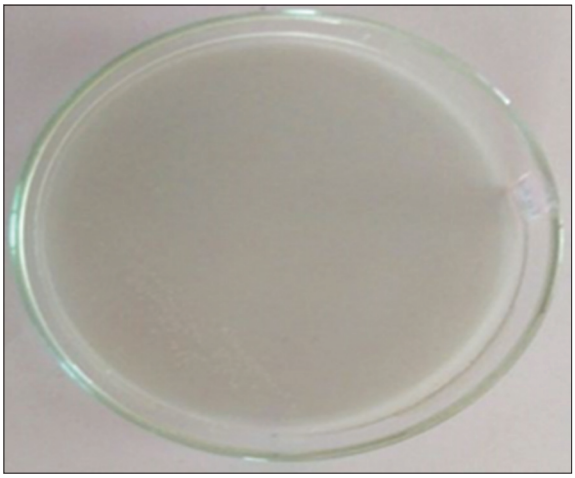

Fig. 6: Mucoadhesive buccal patch

Table 8: Evaluation of performance parameters–drug content uniformity, measurement of bio-adhesion time, and bio-adhesion strength of losartan potassium mucoadhesive buccal patch

Formulation code	Drug content uniformity	*Ex-vivo* bioadhesion strength (gram)	*Ex-vivo* bioadhesion time (hours and minutes)
F1	99.74±0.12	20.26±0.14	7 h 50 min
F2	99.10±0.21	26.18±0.12	8 h 45 min
F3	98.08±0.16	31.25±0.13	7 h 55 min
F4	99.19±0.15	33.76±0.14	8 h 50 min
F5	99.41±0.25	37.62±0.25	9 h 5 min

Table 9: Evaluation of performance parameters–*Ex-vivo* permeation study of losartan potassium mucoadhesive buccal patches

Form code	Time (min)								
	0	60	120	180	240	300	360	420	480
F1	0	18.23	22.16	34.25	41.95	50.86	61.74	76.90	84.22
F2	0	20.12	31.87	39.01	46.45	50.21	58.44	66.18	79.24
F3	0	15.31	24.86	33.29	41.78	52.11	60.79	69.82	76.11
F4	0	18.12	30.12	39.45	48.36	52.14	62.74	66.05	74.54
F5	0	17.25	26.17	33.11	46.10	54.79	59.26	63.19	75.47

Table 10: Regression analysis of the *in-vitro* release data of losartan potassium mucoadhesive buccal patches according to various release kinetic models

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas	
				R^2	N
F1	0.9964	0.9427	0.944	0.8153	0.8153
F2	0.9936	0.9125	0.9524	0.9994	0.8297
F3	0.9926	0.8998	0.9529	0.9993	0.8475
F4	0.9864	0.8856	0.9588	0.9972	0.833
F5	0.9959	0.9262	0.9435	0.9955	0.8115

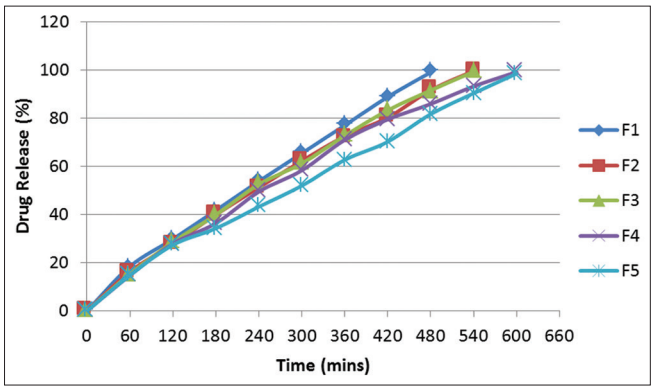

Fig. 7: *In vitro* release graph of patches, mean of three observation ±standard deviation (n=3)

deviation of all the batches was very less and within the limits. Table 8 represents the values.

Ex-vivo bioadhesion strength

All the batches showed good mucoadhesive strength. The results were shown in Table 8. The mucoadhesive strength of the formulations increased with an increase in the concentration of the mucoadhesive polymers. The biological membrane used in the study, molecular mass, and swelling rate of polymers present in the formulation will affect the strength of mucoadhesion. Maximum strength bioadhesion was observed for F5 (37.62±0.25 g) and a minimum for F1 (20.26±0.14 g).

Ex-vivo bioadhesion time

The buccoadhesion time was evaluated and reported in Table 8. Maximum buccoadhesion time was shown by formulation F5 which was 9 h 5 min and minimum bioadhesion time was 7 h 50 min by F1. It indicates that the patches will be resided on mucosa for sufficient time.

Ex-vivo permeation study

The *ex-vivo* drug permeation studies were performed using sheep buccal mucosa as a model membrane using Franz diffusion cell. The study was conducted at 37±2°C for 8 h. The result that the *ex-vivo* drug permeation study is shown in Table 9. It was observed that, as the polymer content increased, the percentage drug permeation decreased. It was found that the drug has a better ability to cross the buccal barrier at a faster rate.

In vitro dissolution study

The data obtained from the *in vitro* drug release study performed up to 8 h gives a clear indication that prepared patches showed a necessary controlled release profile. The results for release studies are shown in Fig. 7.

In vitro drug release kinetics

For all the formulations, various kinetic models were applied and results were interpreted. Based on kinetic assessment, the values were obtained and the best-fitted model was decided. Data are shown in Table 10. Comparison of R^2 values obtained by zero-order, first order, and Higuchi kinetic equation revealed that in vitro drug release followed zero-order kinetics as the R^2 values obtained by zero-order kinetic equation were close to unity. From the "n" value, it can be said that the drug release mechanism from the patch is diffusion with swelling of the polymer.

Table 11: Stability data of formulation F5 in human saliva

Time (h)	Color change	Thickness	Change in pH	Collapsing
0	No change	0.16	No change	No change
1	No change	0.17	No change	No change
2	No change	0.20	No change	No change
4	No change	0.22	No change	No change
6	No change	0.25	No change	No change
8	No change	0.26	No change	No change

Stability studies

The stability of the optimized buccal formulation in human saliva was performed. The results are shown in Table 11. The following parameters such as color change, thickness, change in pH, and collapsing were determined for an interval of about 0, 2, 4, 6, and 8 h.

CONCLUSION

In the present study, an attempt has been done to develop a novel mucoadhesive drug delivery system for the release of losartan potassium in a unidirectional manner, to keep constant therapeutic levels of the drug for a long time. The above study confirmed the probability of designing and developing mucoadhesive patches of losartan potassium using jackfruit gum, which will more ideal than traditional drug delivery. The patches of losartan potassium have appropriate folding endurance, moisture content, and moisture uptake, swelling index, bioadhesion strength, and time. It can also be chosen as a system for the controlled delivery of antihypertensive drugs.

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AUTHORS' CONTRIBUTIONS

We herewith submit a manuscript entitled: "Development, evaluation, and characterization of losartan potassium buccal patches using jackfruit polymer" author by Soji S and Arun J L for consideration for publication as a research paper in the Asian Journal of Pharmaceutical and Clinical Research. Soji S carried out the whole experiment and Arun J L designed the whole research work and carried out the supervision of experiments.

CONFLICTS OF INTEREST

The authors confirmed that there were no conflicts of interest to publish the present article.

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